UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER OF PATENTS AND TRADEMARKS
Washington, D.C. 20231
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
08/914,332	07/15/1997	SCOTT W. VAN ARSDELL	04599/005001	8315

7590 04/22/2003

MARK E. WADDELL, ESQ.
BRYAN CAVE LLP
245 PARK AVENUE
NEW YORK, NY 10167-0034

EXAMINER	
RAMIREZ, DELIA M	

ART UNIT	PAPER NUMBER
1652	35

DATE MAILED: 04/22/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	08/914,332	VAN ARSDELL ET AL.	
	Examiner	Art Unit	
	Delia M. Ramirez	1652	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on *21 February 2003* .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-31* is/are pending in the application.

4a) Of the above claim(s) *23-31* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-22* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *21 February 2003* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☒ Other: *Abstract* .

DETAILED ACTION

Status of the Application

Claims 1-31 are pending.

Applicant's amendment of claims 1, 2, 6, 11, 13, 17-18, 21, and an amendment to the specification in Paper No. 34, filed on 2/21/2003 is acknowledged.

As indicated in previous Office Action Paper No. 33, mailed on 8/13/2002, claims 23-31 were withdrawn from further consideration by the Examiner, 37 CFR 1.142(b), as being drawn to an invention non-elected without traverse in Paper No. 10, filed 11/19/1998. A complete reply to the final rejection must include cancellation of non-elected claims or other appropriate action (37 CFR 1.144) See MPEP § 821.01.

Rejections and/or objections not reiterated from previous office actions are hereby withdrawn.

Specification

1. Applicants have submitted an amendment to the specification to indicate the location of the depository of the biological deposit. It is noted however that this amendment could not be entered since the location provided by Applicants in regard to the insertion of the paragraph is not consistent with what is in page 8. For example, there is no Table in page 8 nor there is a paragraph ending on line 14. Furthermore, the address of the American Type Culture Collection is incorrect. The new address is 10801 University Boulevard, Manassas, VA 20110-2209. Therefore, for the reasons indicated above, the previous objection in regard to the specification is maintained. Appropriate correction is required.

2. The specification is objected to because parts of Appendix I , Table 4, 6, and 7 are not legible. Since the upper margins of Appendix I and Tables 4, 6, and 7 were too narrow, parts of the text have been lost when the corresponding pages were perforated. Applicants are requested to submit a copy of such Appendix and Tables with the appropriate margins to avoid perforation of text. Appropriate correction is required.

Drawings

3. The formal drawings submitted on 2/21/2003 have been reviewed and are approved by a draftsperson under 37 CFR 1.84 or 1.152.

Claim Objections

4. Claim 11 is objected because of the following informalities: for clarity, it is suggested that commas be inserted immediately after the term "step" and immediately after the term "gene". Appropriate correction is required.

5. Claim 11 was objected to because of the recitation of "bioA" since abbreviations unless otherwise obvious and/or commonly used in the art should not be recited in the claims without at least once reciting the entire phrase for which the abbreviation is used.

6. Applicants argue that the term "bioA" refers to a gene and therefore it is not an abbreviation. As such, Applicants argue that this objection should be withdrawn.

7. This objection is hereby withdrawn for the following reasons. The Examiner acknowledges that the term "bioA" refers to a gene and it is not an abbreviation. However it is noted that gene nomenclature may be species-specific, therefore if the product it encodes is not

recited, the term "bioA" is considered indefinite for the reasons discussed below in claim rejections under 35 USC 112, second paragraph.

Claim Rejections - 35 USC § 112, Second Paragraph

8. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

9. Claim 11 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. This rejection is applied in view of Applicant's response in regard to a previous claim objection as discussed above.

10. Claim 11 is indefinite in the recitation of "bioA gene is deregulated in said bacterium" for the following reasons. While the term "bioA" is appropriate nomenclature for a gene encoding 7,8 DAPA aminotransferases in organisms like E. coli or Bacillus, the use of this nomenclature for genes encoding proteins of identical function in other organisms may not be accurate. As known in the art, genes encoding proteins of identical function in two different organisms may use different designations. For example, the BIO3 gene in S. cerevisiae encodes a 7,8 DAPA aminotransferase. See the abstract of Phalip et al. (Gene 232:43-51, 1999). As such, the use of gene terminology which is applicable to some organisms and not to others is confusing since the claim uses this gene nomenclature with respect to any bacteria. For examination purposes, the term "bioA" will be interpreted as "gene encoding a DAPA aminotransferase". If Applicants wish to use the recited terminology in the claims, it is suggested that the claim be either amended

to clearly indicate the organism associated with the specific gene designation or amended to indicate the gene product encoded. Correction is required.

Claim Rejections - 35 USC § 112, First Paragraph

11. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

12. Claims 1-22 remain rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

13. This rejection has been discussed at length in Paper No. 33, mailed 8/13/2002.

14. Applicants argue that the specification provide specific definitions for the terms "lysine-utilizing DAPA aminotransferase" and "SAM-utilizing DAPA aminotransferase", therefore those definitions alone should be sufficient to indicate that Applicants were in possession of the claimed invention. Applicants submit that the specification discloses engineered B. subtilis and E. coli strains, how to identify a lysine-utilizing DAPA aminotransferase, an assay to detect DAPA aminotransferase activity, an assay to detect which enzymes are lysine-utilizing or SAM-utilizing DAPA aminotransferases, how to deregulate lysine production, mutations which deregulate lysine production and bacteria having deregulated lysine production, and deregulation of a biotin synthetic step. Applicants further submit that the specification provides ample background information regarding the biosynthesis of biotin vitamers in numerous bacteria such

as E. coli, S. typhimirium, B. subtilis, and B. sphaericus as well the genetic aspects of the bio operon in E. coli, B. subtilis and B. sphaericus. Applicants also argue that six strains have been deposited which should be sufficient to show possession of the claimed invention. Furthermore, Applicants contend that the claims are drawn to a method and not to a composition of matter. Applicants direct the Examiner's attention to Example 18 in the "Revised Interim Written Description Guidelines Training Materials" and conclude that based on the analysis discussed in Example 18, the present claims are in full compliance with the written description requirement.

15. Applicant's arguments have been fully considered but are not deemed persuasive to overcome the rejection. While the Examiner acknowledges that the specification provides (1) specific definitions for the terms "lysine-utilizing DAPA aminotransferase" and SAM-utilizing DAPA aminotransferase, (2) engineered B. subtilis and E. coli strains, (3) an assay to detect DAPA aminotransferase activity, (4) an assay to detect which enzymes are lysine-utilizing or SAM-utilizing DAPA aminotransferases, (5) how to deregulate lysine production in B. subtilis, (6) mutations which deregulate lysine production in B. subtilis, (7) Bacillus strains having deregulated lysine production and deregulation of a biotin synthetic step, (8) background information regarding the biosynthesis of biotin vitamers in numerous bacteria as well the genetic aspects of the bio operon in E. coli, B. subtilis and B. sphaericus, and the deposit of six strains, the claimed invention is not adequately described for the following reasons. The claimed method requires culturing a bacterium comprising a genus of lysine-utilizing DAPA aminotransferases, however the specification provides only one lysine-utilizing DAPA aminotransferase from B. subtilis and the prior art at the time the application was filed does not provide any additional information and/or suggestion as to other bacteria comprising lysine-

utilizing DAPA aminotransferases or polynucleotides encoding said aminotransferases which could be used to transform any bacterial host cell.

The Examiner agrees that the specification provides an assay to detect lysine-utilizing DAPA aminotransferase activity but disagrees with Applicant's contention that the specification provides information as to how to identify any lysine-utilizing DAPA aminotransferase since it does not provide the critical structural elements required in a polynucleotide/polypeptide to have lysine-utilizing DAPA aminotransferase activity. The Examiner is well aware that the claims are directed to a method and not to a composition of matter but ,as already discussed in previous Office Action Paper No. 33, adequate description of a method would also require adequate description of essential matter which is required to practice the claimed method. Applicants refer to Example 18 and submit that such example is analogous to the instant case, however the Examiner disagrees with Applicant's contention since in that Example, the essential matter required to practice the claimed invention, i.e. Neurospora crassa mitochondria, was adequately described. In the instant case, the essential matter to practice the claim method is a bacterium comprising a lysine-utilizing DAPA aminotransferase and/or the polynucleotide encoding a lysine-utilizing DAPA aminotransferase to transform a bacterium. The claims are directed to a method wherein a bacterium comprises any lysine-utilizing DAPA aminotransferase, and while the specification discloses 6 strains which have been deposited, the strains deposited contain B. subtilis lysine-utilizing DAPA aminotransferase only. Therefore, in view of the information provided, it is unclear as to how one of skill in the art can reasonably conclude that the method claimed is adequately described.

16. The instant rejection may be overcome by limiting the claims to a B. subtilis lysine-utilizing DAPA aminotransferase.

17. Claims 1-22 remain rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method for the production of biotin vitamers using a bacterial cell comprising B. subtilis lysine-utilizing DAPA aminotransferases and wherein the lysine or biotin synthesis in said bacterial cell is deregulated by mutations in the genes encoding aspartokinase I, II, III or DAP decarboxylase, does not reasonably provide enablement for practicing the claimed method with a bacterial cell comprising any lysine-utilizing DAPA aminotransferase. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

18. This rejection has been discussed at length in Paper No. 33, mailed 8/13/2002.

19. Applicants argue that the previous Examiner of record acknowledged in an Office Action mailed on 2/1/1999 that the specification is enabling for a method of producing a biotin vitamer by culturing a bacterium comprising a lysine-utilizing DAPA aminotransferase in an environment enriched for lysine or a lysine analog. Therefore, Applicants submit that this exact issue has already been fully addressed in prior prosecution. Furthermore, Applicants argue that the same rejection was made by the previous Examiner of record and that the Examiner after an interview with Dr. John Perkins (co-inventor) and Mr. Kevin Cooper agreed to withdraw the enablement rejection upon identification of the deposited strains BI282, B1603, BI90 and BI96. Therefore, it is Applicant's opinion that the current rejection for lack of enablement regarding

bacteria that are deregulated in at least one biotin synthetic step other than bioA expression has been fully addressed and overcome in prior prosecution. In addition, Applicants submit that the previous Examiner of record required that a deposit of strains which are resistant to AEC be made and that the specification discloses the deposit of strains BI641 and BI642, which are mutants strains resistant to AEC. Therefore, it is Applicant's opinion that the current rejection for lack of enablement regarding bacteria that are deregulated for lysine production and bacteria that express a SAM-utilizing DAPA aminotransferase has been also fully addressed and overcome in prior prosecution.

Applicants contend that the Examiner has not indicated why admissions made by the previous Examiner of record in regard to enablement are no longer applicable. Applicants argue that considerable effort and expense has been incurred on the part of Applicants in a lengthy prosecution process and indicate that the present Examiner should give the previous determinations by the PTO full faith and credit. Applicants submit that the Examiner has misconstruct the claims and that the claims are not directed to any microorganism but to a method of producing a biotin vitamer by culturing a bacterium containing certain identified enzymes. According to Applicants, the specification provides detailed information as discussed above in regard to the written description rejection, which would enabled one of skill in the art to practice the claimed invention without undue experimentation. Therefore, it is Applicant's opinion that the rejection should be withdrawn.

20. Applicant's arguments have been fully considered but are not deemed persuasive to overcome the rejection. The Examiner acknowledges the issues and/or rejections previously addressed by the previous Examiner of record and acknowledges Applicant's opinion in regard

to the duration of prosecution of the instant application, however it is noted that previous delays in the prosecution of the instant application were beyond the present Examiner's control. While the Examiner has given full faith and credit to previous determinations by the PTO, it is noted that the present Examiner must examine the instant application according to the guidelines set forth by the USPTO as well as the MPEP.

In regard to arguments that the Examiner has misconstruct the claims, it is reiterated that the Examiner is well aware that the claims are not drawn to any microorganism but to a method, however it is noted that enablement of the claimed method requires enablement of essential matter required to practice the claimed method. The Examiner acknowledges the information provided by Applicants in the specification as detailed above, however the specification is not deemed enabling for the full scope of the claimed invention for the following reasons.

The claimed method requires culturing a bacterium comprising any lysine-utilizing DAPA aminotransferases, however the specification provides only one lysine-utilizing DAPA aminotransferase from B. subtilis and the prior art at the time the application was filed does not provide any additional information and/or suggestion as to other bacteria comprising lysine-utilizing DAPA aminotransferases or polynucleotides encoding said aminotransferases which could be used to transform any bacterial host cell.

As indicated above, the Examiner disagrees with Applicant's contention that the specification provides information as to how to identify any lysine-utilizing DAPA aminotransferase since it does not provide the critical structural elements required in a polynucleotide/polypeptide to have lysine-utilizing DAPA aminotransferase activity. While it is acknowledged that Applicants have deposited strains comprising a lysine-utilizing DAPA

aminotransferase, such aminotransferase is from B. subtilis only. As indicated in previous Office Action Paper No. 33, attempting to isolate polynucleotides encoding polypeptides of similar function using structural homology is unpredictable as evidenced by Bork, Van de Loo et al., and Broun et al. already discussed. In view of the information provided, the lack of information as to the critical structural elements required in a polynucleotide/polypeptide to display lysine-utilizing DAPA aminotransferase activity and the unpredictability of the art in regard to isolating such polynucleotides/polypeptides using structural homology, it is unclear as to how one of skill in the art can reasonably conclude that the specification provides enablement for the full scope of the claims.

21. It is noted that the instant rejection may be overcome by limiting the claims to a B. subtilis lysine-utilizing DAPA aminotransferase.

Claim Rejections - 35 USC § 102

22. Claims 1, 3, 7, 11-19, 21-22 remain rejected under 35 U.S.C. 102(b) as being anticipated by Bower et al. (EP-0-635-572-A2, 1995; cited in the IDS).

23. This rejection has been discussed at length in Paper No. 33, mailed 8/13/2002.

24. Applicants argue that each and every element recited in the claims must be found in the a prior art reference, the Examiner should identify wherein each and every facet of the claimed invention is disclosed in the prior art reference and that all words in a claim must be considered. Applicants submit that Bower does not disclose that lysine, a lysine analog or a lysine precursor is added to the bacterial culture and that Bower does not disclose the exogenous addition of

lysine, a lysine analog or a lysine precursor during the entire culturing step. Therefore, it is Applicant's opinion that the rejection should be withdrawn.

25. Applicant's arguments have been fully considered. In view of Applicant's amendment of the claims which now recite "during the entire culturing step", this rejection is hereby withdrawn since Bower et al. does not teach a method for the production of a biotin vitamer by culturing a bacterium comprising a lysine-utilizing DAPA aminotransferase wherein said culturing requires the addition of lysine, lysine analogs or lysine precursors during the entire culturing step.

26. Claims 1, 3, 7, 11-19, 21-22 remain rejected under 35 U.S.C. 102(e) as being anticipated by Bower et al. (U.S. Patent No. 6057136, July 8, 1996).

27. This rejection has been discussed at length in Paper No. 33, mailed 8/13/2002.

28. Applicants argue that since the teachings of Bower et al. above and the instant reference are substantially similar, the same arguments set forth above would also apply to the instant rejection.

29. Applicant's arguments have been fully considered. In view of Applicant's amendment of the claims which now recite "during the entire culturing step", this rejection is hereby withdrawn since Bower et al. does not teach a method for the production of a biotin vitamer by culturing a bacterium comprising a lysine-utilizing DAPA aminotransferase wherein said culturing requires the addition of lysine, lysine analogs or lysine precursors during the entire culturing step.

Claim Rejections - 35 USC § 103

30. Claims 8 and 20 remain rejected under 35 U.S.C. 103(a) as being unpatentable over Bower et al. (EP-0-635-572-A2, 1995; cited in the IDS) in view of Yamada et al. (U.S. Patent No. 4563426, 1986).

31. This rejection has been discussed at length in Paper No. 33, mailed 8/13/2002.

32. Applicants submit that the arguments presented above with respect to Bower et al. apply to the obviousness rejection as well since claims 8 and 20 depend from claim 1 or 2. According to Applicants, claims 1 and 2 have been amended and that the limitations in such claims are not anticipated by Bower et al. or Yamada. Applicants also argue that the motivation provided by the Examiner is not the evidence required to combine documents. Applicants argue that the motivation or suggestion to make the proposed combination must be found in the documents themselves or recognized in the art.

33. Applicant's arguments have been fully considered. In view of Applicant's amendment of the claims which now recite "during the entire culturing step", this rejection is hereby withdrawn since neither Bower et al. nor Yamada et al. combined teach a method for the production of a biotin vitamer by culturing a bacterium comprising a lysine-utilizing DAPA aminotransferase wherein said culturing requires the addition of lysine, lysine analogs or lysine precursors during the entire culturing step.

Conclusion

34. No claim is in condition for allowance.

35. Applicant's amendment of claim 1, 2, 6, 11, 13, 17-18, 21 and/or response, necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

36. Applicants are requested to submit a clean copy of the pending claims (including amendments, if any) in future written communications to aid in the examination of this application.

37. Certain papers related to this application may be submitted to Art Unit 1652 by facsimile transmission. The FAX number is (703) 308-4556. The faxing of such papers must conform with the notices published in the Official Gazette, 1156 OG 61 (November 16, 1993) and 1157 OG 94 (December 28, 1993) (see 37 CFR 1.6(d)). NOTE: If Applicant submits a paper by FAX, the original copy should be retained by Applicant or Applicant's representative. NO DUPLICATE COPIES SHOULD BE SUBMITTED, so as to avoid the processing of duplicate papers in the Office.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Delia M. Ramirez whose telephone number is (703) 306-0288. The examiner can normally be reached on Monday-Friday from 8:30 AM to 5:00 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Dr. Ponnathapura Achutamurthy can be reached on (703) 308-3804. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

Delia M. Ramirez, Ph.D.
Patent Examiner
Art Unit 1652

DR
April 17, 2003